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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	21

Application Number	09/775,181
Filing Date	02/01/01
First Named Inventor	Donoho
Group Art Unit	1646
Examiner Name	R. Li
Attorney Docket Number	LEX-0129-USA

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Supplemental Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
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- ☐ After Allowance Communication to Group
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- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
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- ☐ Status Letter
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  - Return Postcard

Remarks

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PATENT TRADEMARK OFFICE

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature	Lance K Ishimoto Reg. No. 41,866 Peter G Soferian
Date	August 1, 2003

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313 on this date: August 1, 2003

Typed or printed name	Nancy Stacey		
Signature	Nancy Stacey	Date	August 1, 2003

#19
APP
8/18/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Donoho *et al.*	Group Art Unit: 1646
Application No.:	09/775,181	Examiner: R. Li
Filed:	02/01/01	
Title: Novel Human Membrane Proteins and Polynucleotides Encoding the Same		Atty. Docket No.: LEX-0129-USA

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED MARCH 6, 2003

Commissioner for Patents
Alexandria, VA 22313

Sir:

Applicants acknowledge the receipt of the Office Action ("the Action") mailed on March 6, 2003 (Paper No. 17), which has been carefully reviewed and studied. The Examiner is respectfully requested to reexamine and reconsider the application in view of the following remarks. In order to facilitate the Examiner's evaluation of the application, Applicants have attempted to address the objections and rejections in Paper No. 17 in the same order in which they were originally raised.

A Petition for an Extension of Time of two months to and including August 6, 2003 and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(1) from Applicants' representatives Deposit Account are included. The response is thus timely filed. Applicants believe no fees in addition to the fee for the extension of time are due in connection with this response. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-0892.

RESPONSE

I. Status of the Claims

Claims 1-8 are pending and rejected under 35 U.S.C. § 101. As per revised 37 CFR 1.121, the claims and their current status are listed in **Exhibit A**.

II. Rejection of Claims 1-8 Under 35 U.S.C. § 101

The Action maintains the rejection of claims 1-8 under 35 U.S.C. § 101 because allegedly the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility. Applicants respectfully persist in their traverse.

In Applicants' response accompanying Applicants' Request for Continued Examination (RCE) filed on 1/16/03 Applicants submitted information that a knockout mouse had been made in which the mouse gene homologous to that represented by SEQ ID NOS: 1 and 2 had been disrupted by homologous recombination. When these knockout mice were subject to a medical work-up it was determined that male homozygous mutant mice exhibited increased mean body fat, triglyceride and cholesterol levels when compared to their gender-matched wild-type littermates and historical means. The Action stated that this evidence was not presented in an appropriate form and should the Examiner feel such is necessary, Applicants will submit a declaration regarding these findings, their medical significance and their relationship to heart disease. However, it is Applicants' assertion that the association between obesity, heart disease and blood lipid levels is extremely well known to those of skill in the art. In fact, the clear and convincing utility of information regarding lipid and cholesterol metabolism and its application to the very real world utility of predicting heart and coronary disease was the basis of the awarding of the 1985 Nobel Prize in Physiology and Medicine.

Applicants respectfully submit that the present question is not the relationship between obesity, elevated blood lipids and heart disease (for this is widely accepted), but one regarding the utility of the present invention. Would those of skill in the art recognize the utility of present invention? It is Applicants' position that indeed they would.

Applicants invite the Examiners' attention to the fact that when the invention was used as described in the specification, it yielded the results asserted in the specification. Specifically, the

specification describes an invention (the sequences which encode a novel human GPCR) that when used as described in the specification, to make a knockout mouse (as described on pages 2 and 29), provides evidence that the asserted role of the protein of the present invention in heart and coronary disease, and obesity (as described in the specification on page 57, line 3) was accurate. Thus, when the invention was used as described in the specification, it performed as predicted in the specification, to have utility directly linked to the asserted real world, highly significant, medical disorders of heart and coronary disease, and obesity.

Therefore, the sequences of the present invention have, as described throughout the specification, clear utility in the diagnosis of heart and coronary disease, the development of drugs (reverse agonists or antagonists, antibodies, etc.) directed at the treatment of obesity, heart and coronary disease as well as the monitoring of clinical trials for drugs directed at such disorders. Thus, clearly the sequences of the present invention have utility that is specific, substantial and real world.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions as described in the specification. As evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided as **Exhibit B**. This is the result of overlaying the sequence of SEQ ID NO:1 of the present invention and the identified human genomic sequence. By doing this, one is able to identify the portions of the genome that encode the present invention. If these regions of the genome are non-contiguous, this is indicative of individual exons. The results of such an analysis indicates that the sequence of the present invention is encoded by 11 exons spread non-contiguously along a region of human chromosome 10. Thus clearly one would not simply be able to identify the 11 or more protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to accurately map the protein encoding regions identified specifically by the sequences of the present invention without knowing

exactly what those specific sequences were.

Therefore, clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome.

An additional utility includes the use of the presently claimed polynucleotides on DNA chips. Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that

such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see,

e.g., Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). The sequences of the present invention have particularly specific utility in DNA gene chip based analysis as they have been identified to contain several coding region nucleotide polymorphisms (see above), thus increasing their utility in DNA gene chip based analysis.

Finally, the Examiner is requested to consider the issue of due process. Applicants understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter. As the issued U.S. Patents cited above are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph, Applicants respectfully submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101.

Thus in summary, Applicants submit that the presently claimed molecules have been shown to

have utility in the diagnosis of heart and coronary disease, the development of drugs (reverse agonists or antagonists, antibodies, etc.) directed at the treatment of obesity, heart and coronary disease as well as the monitoring of clinical trials for drugs directed at such disorders. These utilities are clearly specific, substantial credible, well-established and real world utilities. The invention when used as described in the specification, yielded results consistent with the utilities that had been described in the specification, utilities linked to the real world highly significant medical disorders of heart and coronary disease, and obesity. Therefore, Applicants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible, real world and well-established utility, the rejection of the claims under 35 U.S.C. § 101 has been overcome. Thus, Applicants respectfully request that the rejection be withdrawn.

III. Rejection of Claims 1-8 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-8 under 35 U.S.C. § 112, first paragraph, since the claimed invention is not supported by either a specific substantial and credible utility, or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully submit that claims 1-8 have been shown to have "a specific, substantial, and credible utility", as detailed in the section above. Therefore, one skilled in the art would clearly know how to use the claimed invention and Applicants therefore request that the rejection of claims. Therefore, Applicants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, and thus the rejection of the claims under 35 U.S.C. § 112, first paragraph has been avoided. Thus, Applicants respectfully request that the rejection be withdrawn.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Li have any questions or comments, or

believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

August 1, 2003
Date

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Agent for Applicants

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